Chromosome segregation model - detailed description

March 28, 2012

Introduction

This is a more detailed version of the kinetochore segregation model to be published in the JCB article, which should be referred to for all the experimental, biological and non-technical aspects of this work.

1 Definitions

1.1 State vector

The mitotic spindle is described by the speeds and position along the x axis of two spindle pole bodies, N chromosomes with two centromeres and M_k attachment sites per centromere.

Positions are noted as follow:

- The left and right spindle pole bodies (SPBs), x_s^L and x_s^R
- The N centromeres, x_n^A, $x_n^B, n \in \{1, \cdots, N\}$
- The M_k attachment sites of each centromere, x_{nm}^A, $x_{nm}^B, n \in \{1, \cdots, N\}, m \in \{1, \cdots, M_k\}$

The speeds are noted with a dot: $dx/dt = \dot{x}$.

As all the interactions are assumed to be parallel to the spindle axis, only the positions along this axis are considered, in a coordinate system with its origin at the center of the spindle, which means that $x_s^L(t) = -x_s^R(t) \, \forall t$.

The following force balances are considered:

1.1.1 Forces at the right SPB :

- Friction forces (viscous drag): $F_s^f = -\mu_s \dot{x_s}^R$
- Midzone force generators (applied at the right SPB):

$$F_{mid} = F_z \left(1 - (\dot{x}_s^R - \dot{x}_s^L)/V_z\right) = F_z \left(1 - 2\dot{x}_s^R/V_z\right)$$

- Total kinetochore microtubules force generators:

$$\begin{aligned}
F_{kMT}^T = \sum_{n=1}^{N} \sum_{m=1}^{M_k} & - \rho_{nm}^A \, F_k \left(1 - (\dot{x}_{nm}^A - \dot{x}_s^R)/V_k\right) \\
& + \lambda_{nm}^A \, F_k \left(1 - (\dot{x}_{nm}^A + \dot{x}_s^R)/V_k\right) \\
& - \rho_{nm}^B \, F_k \left(1 - (\dot{x}_{nm}^B - \dot{x}_s^R)/V_k\right) \\
& + \lambda_{nm}^A \, F_k \left(1 - (\dot{x}_{nm}^B + \dot{x}_s^R)/V_k\right)
\end{aligned}$$

1.1.2 Forces at centromere An

- Drag: $F_c^f = -\mu_c \dot{x_n}^A$
- Cohesin bond (Hook spring) restoring force exerted by centromere B:

$$F_{BA} = -\kappa_c (x_n^A - x_n^B - d_0), \text{with } F_{BA} = -F_{AB}$$

- Total visco-elastic bond between the centromere A and the attachment sites:

$$F_v^T = \sum_{m=1}^{M_k} -\kappa_k (x_n^A - x_{nm}^A) - \mu_k (\dot{x}_n^A - \dot{x}_{nm}^A)$$

1.1.3 Forces at attachment site Anm

- Visco-elastic bond between the centromere A and the attachment sites:

$$F_v = \kappa_k (x_n^A - x_{nm}^A) + \mu_k (\dot{x}_n^A - \dot{x}_{nm}^A)$$

- Kinetochore microtubules force generators:

$$F_{kMT}^A = \rho_{nm}^A \, F_k \left(1 - (\dot{x}_{nm}^A - \dot{x}_s^R)/V_k\right) - \lambda_{nm}^A \, F_k \left(1 - (\dot{x}_{nm}^A - \dot{x}_s^L)/V_k\right)$$

Here, ρ_{nm}^A and λ_{nm}^A are two random variables that govern the attachment state of the site x_{nm}^A, such that:

$$\rho_{nm}^A = \begin{cases} 1 & \text{if the site is attached to the right SPB} \\ 0 & \text{otherwise} \end{cases} \tag{1}$$

$$\lambda_{nm}^A = \begin{cases} 1 & \text{if the site is attached to the left SPB} \\ 0 & \text{otherwise} \end{cases} \tag{2}$$

Note that ρ_{nm}^A and λ_{nm}^A are not independent, as an attachment site can't be attached to both poles. To take this into account, we can define the variable $p_{nm}^A = \rho_{nm}^A - \lambda_{nm}^A$ such that:

$$p_{nm}^A = \begin{cases} -1 & \text{if the site is attached to the left SPB} \\ 0 & \text{if the site is not attached} \\ 1 & \text{if the site is attached to the right SPB} \end{cases} \tag{3}$$

We have:

$$\lambda_{nm}^A = p_{nm}^A \left(p_{nm}^A - 1\right)/2 \tag{4}$$

$$\rho_{nm}^A = p_{nm}^A \left(p_{nm}^A + 1\right)/2 \tag{5}$$

We also define N_n^{AL} and N_n^{AR} as the number of ktMTs of centromere A attached to the left and right SPBs, respectively:

$$N_n^{AL} = \sum_{m=1}^{M_k} \lambda_{nm}^A \text{ and } N_n^{AR} = \sum_{m=1}^{M_k} \rho_{nm}^A \tag{6}$$

Note that $N_n^{AL} + N_n^{AR} \leqslant M_k \, \forall \, p_{nm}$ The same definitions apply for the centromere B and left SPB.

1.2 Set of first order coupled equations

In the viscous nucleoplasm, inertia is negligible. Newton first principle thus reduces to: $\sum F = 0$, all the equations are gathered together in the system of equations:

$$\mathbf{A}\dot{X} + \mathbf{B}X + C = 0$$

The vector X has $1 + 2N(M_k + 1)$ elements and is defined as follow:

$$X = \{x_s^R, \{x_n^A, \{x_{nm}^A\}, x_n^B, \{x_{nm}^B\}\}\} \text{ with } n \in 1 \cdots N \text{ and } m \in 1 \cdots M_k$$

With this order, the index of the n^{th} centromere A, noted i_n^A is given by $i_n^A = 2n(M_k + 1) + 2$. Similarly, we have:

$$\begin{aligned} i_n^B &= 2n(M_k + 1) + M_k + 3 \\ i_{nm}^A &= 2n(M_k + 1) + 3 + m \\ i_{nm}^B &= 2n(M_k + 1) + M_k + 4 + m \end{aligned}$$

To simplify the equations, we set F_k as unit force and V_k as unit speed, thus $F_k/V_k = 1$. From the above we have:

$$\begin{aligned} A &= \begin{pmatrix} a_{1,1} & \cdots\cdots & a_{1,i_{nm}^A} & \cdots\cdots & a_{1,i_{nm}^B} \\ \cdots\cdots & a_{i_n^A,i_n^A} & a_{i_n^A,i_{nm}^A} & \cdots\cdots & \\ a_{i_{nm}^A,1} & a_{i_{nm}^A,i_n^A} & a_{i_{nm}^A,i_{nm}^A} & \cdots\cdots\cdots\cdots\cdots & \\ \cdots\cdots\cdots\cdots\cdots\cdots\cdots & & & a_{i_n^B,i_n^B} & a_{i_n^B,i_{nm}^B} \\ a_{i_{nm}^B,1} & \cdots\cdots\cdots\cdots\cdots & & a_{i_n^B,i_{nm}^B} & a_{i_{nm}^B,i_{nm}^B} \end{pmatrix} \\ &= \begin{pmatrix} -\mu_s - F_z/V_z - \sum(p_{nm}^A + p_{nm}^B) & \cdots\cdots\cdots & p_{nm}^A & \cdots\cdots\cdots & p_{nm}^B \\ \cdots\cdots\cdots\cdots\cdots\cdots\cdots & -\mu_c - M_k\mu_k & \mu_k & \cdots\cdots\cdots\cdots\cdots & \cdots \\ p_{nm}^A & \mu_k & -\mu_k + p_{nm}^A & \cdots\cdots\cdots\cdots\cdots & \cdots \\ \cdots\cdots\cdots\cdots\cdots\cdots\cdots & \cdots\cdots\cdots\cdots & \cdots\cdots & -\mu_c - M_k\mu_k & \mu_k \\ p_{nm}^B & \cdots\cdots\cdots\cdots & \cdots\cdots & \mu_k & -\mu_k + p_{nm}^B \end{pmatrix}, \end{aligned} \tag{7}$$

$$B = \begin{pmatrix} 0 & \cdots\cdots\cdots\cdots & \cdots\cdots & \cdots\cdots\cdots\cdots & \cdots \\ \cdot\cdot & -\kappa_c - M_k\kappa_k & \kappa_k & \kappa_c & \cdots \\ \cdot\cdot & \kappa_k & -\kappa_k & \cdots\cdots\cdots\cdots & \cdots \\ \cdot\cdot & \kappa_c & \cdots & -\kappa_c - M_k\kappa_k & \kappa_k \\ \cdots\cdots\cdots\cdots & & & \kappa_k & -\kappa_k \end{pmatrix} \quad \text{and} \quad C = \begin{pmatrix} 0 \\ 0 \\ d_0 \\ 0 \\ d_0 \\ 0 \end{pmatrix}$$